New definition for the partial remission period in children and adolescents with type 1 diabetes

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Abstract: OBJECTIVE To find a simple definition of partial remission in type 1 diabetes that reflects both residual beta-cell function and efficacy of insulin treatment. RESEARCH DESIGN AND METHODS A total of 275 patients aged <16 years were followed from onset of type 1 diabetes. After 1, 6, and 12 months, stimulated C-peptide during a challenge was used as a measure of residual beta-cell function. RESULTS By multiple regression analysis, a negative association between stimulated C-peptide and A1C (regression coefficient -0.21, P < 0.001) and insulin dose (-0.94, P < 0.001) was shown. These results suggested the definition of an insulin dose-adjusted A1C (IDAA1C) as A1C (percent) + [4 x insulin dose (units per kilogram per 24 h)]. A calculated IDAA1C < or =9 corresponding to a predicted stimulated C-peptide >300 pmol/l was used to define partial remission. The IDAA1C < or =9 had a significantly higher agreement (P < 0.001) with residual beta-cell function than use of a definition of A1C < or =7.5%. Between 6 and 12 months after diagnosis, for IDAA1C < or =9 only 1 patient entered partial remission and 61 patients ended partial remission, for A1C < or =7.5% 15 patients entered partial remission and 53 ended, for a definition of insulin dose < or =0.5 units . kg(-1) . 24 h(-1) 5 patients entered partial remission and 66 ended, and for stimulated C-peptide (>300 pmol/l) 9 patients entered partial remission and 49 ended. IDAA1C at 6 months has good predictive power for stimulated C-peptide concentrations after both 6 and 12 months. CONCLUSIONS A new definition of partial remission is proposed, including both glycemic control and insulin dose. It reflects residual beta-cell function and has better stability compared with the conventional definitions.

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New Definition for the Partial Remission Period in Children and Adolescents with T1D

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Objective-To find a simple definition of partial remission (PR) in T1D that reflects both residual beta-cell function and efficacy of insulin treatment.

Research Design and Methods-275 patients <16 years were followed from onset of T1D. After 1, 6 and 12 months stimulated C-peptide during a challenge was used as a measure of residual beta-cell function.

Results-By multiple regression analysis a negative association between stimulated C-peptide and HbA1c (-0.21, regression coefficient, p<0.001) and insulin dose (-0.94, regression coefficient, p<0.001) was shown. These results suggested the definition of an insulin dose-adjusted HbA1c (IDAA1c) as: HbA1c (%) + [4 x insulin dose (U/Kg/24h)]. A calculated IDAA1c ≤ 9 corresponding to a predicted stimulated C-peptide > 300 pmol/l was used to define PR. The IDAA1c ≤ 9 had a significantly higher agreement (p <0.001) with residual beta-cell function than using a definition of HbA1c ≤ 7.5 %. Between 6 and 12 months after diagnosis, using IDAA1c ≤ 9 only 1 patient entered PR and 61 PR ended; using HbA1c ≤ 7.5 % , 15 entered PR and 53 ended; using a definition of insulin dose ≤ 0.5 U/kg/24h 5 entered and 66 ended and for stimulated C-peptide (>300 pmol/l) 9 entered PR and 49 ended.
IDAA1c at 6 months has good predictive power for stimulated C-peptide concentrations after both 6 and 12 months.

Conclusions-A new definition of PR is proposed including both glycemic control and insulin dose. It reflects residual beta-cell function and has a better stability compared with the conventional definitions.

Clinically, newly diagnosed type 1 diabetes is characterized by a transient partial remission (PR) period (”honeymoon”) starting shortly after insulin treatment is initiated and during which the patient’s need for exogenous insulin treatment declines and in some cases even totally disappears, and metabolic control is near to optimal. The pathogenesis of this has been the subject of discussion (1) but is likely to be a combination of two factors: partial β-cell recovery with improved insulin secretion (2) and improvement of peripheral insulin sensitivity (3).

The definition of the PR period has varied greatly in the past. Most authors define PR as insulin requirements ≤ 0.5U/kg/24h (4-6). However, it is not useful to define a disease state by the treatment applied and insulin dose is influenced by a large number of other factors. At best, this is reasonable when the treatment policy is uniform. This is rarely the case even within single centres and even less so in a multicenter international study. As an extreme consequence of this definition, a diabetic patient is considered to be in PR when treated with a relatively low dose of insulin. To correct for this problem others have used the definition as a HbA_{1c} close to or within the normal range (7). This definition is also influenced by the treatment, as increasing the insulin dose lowers the HbA_{1c} level. Furthermore, there is an initial time delay from the time of diagnosis of 4-6 weeks before a new steady state HbA1c can be achieved (8). Somewhat more relevant is to combine the two definitions, that is, an insulin requirement of ≤ 0.5 U/kg/24h in combination with HbA_{1c} ≤ 7.5 % (9,10). Others have used an even lower limit for insulin requirement such as 0.3U/kg/24h (11). Combining the two parameters is better than using either one alone, but having separate limits on each variable still makes the definition suffer from the problem that a treatment change easily influences the classification of a patient

As another possibility, Komulainen (12) used a basal C-peptide level of 100 pmol/l as an index for residual beta cell function . While fasting C-peptide alone may be relatively easy to obtain in research centres and correlates with stimulated C-peptide it is insufficient for detecting dynamic changes in residual beta-cell function. Serial measurements of stimulated C-peptide which directly reflect residual beta-cell function have therefore become the gold standard for evaluation of endogenous insulin secretion (13) but no definitions of PR has been proposed based on stimulated C-peptide. Besides, determination of stimulated C-peptide is a laborious, expensive and time consuming research tool and unpleasant for the child. The patient has to present fasting, take part in a 90 minute study and delay the morning insulin. Therefore, it would be useful to have an easy clinical measure for the PR somewhat similar to the homeostasis model assessment (HOMA) for insulin resistance and beta-cell function (14). The objective of the current longitudinal investigation was therefore to evaluate the relation between HbA1c and insulin dose, which are both routinely measured in clinical practice, to create a surrogate measure of stimulated C-peptide and near normal glycemia. Furthermore the study aimed to examine the validity and reliability of this measure.

RESEARCH DESIGN AND METHODS

Study subjects: The study was a multicentre longitudinal investigation in 18 paediatric departments representing 15 countries in Europe and Japan. 275 children and adolescents less than 16 years with newly diagnosed type 1 diabetes presenting to the paediatric departments between August 1999 and December 2000, were included in the study. Exclusion criteria were: suspected

non-T1D (MODY, secondary diabetes etc.), and patients initially treated outside of the centres for more than 5 days. Patients were diagnosed according to the World Health Organization (WHO) criteria. Eighty-four percent of the patients were white Caucasian, and the mean ± SD age at clinical diagnosis was 9.1 ± 3.7 yrs; body mass index, 16.5 ± 3.2 kg/m^2; insulin regimens were recorded 1, 3, 6, 9 and 12 months after diagnosis. After 12 months 52.9% of the children were on twice insulin daily, 25% on three times and 18.5% on 4 or more injections. Only a few children (3.3%) received one insulin injection daily. A premixed form of insulin was used in 72.3 % of the children on twice daily insulin. Only 3 children used an insulin infusion pump while 13% were treated with a rapid acting insulin analogue. Mean daily insulin dose: 0.7 ±0.3 U/kg. In order for the new measure to cover different insulin policies local centres were not instructed to follow a specific insulin treatment program.

The study was performed according to the criteria of the Helsinki II Declaration (15) and was approved by the local ethical committee in each centre. All the patients, their parents or guardians gave informed consent.

Methods: ***HbA1c*** **-** Samples for HbA_{1c} analysis were collected at onset and after 1, 3, 6, 9 and 12 months at each department using the Bio-Rad HbA_{1c} sample preparation kit (Bio-Rad Laboratories, Munich, Germany) and mailed to the Steno Diabetes Centre (Denmark) as described before (16). The HbA_{1c} analysis was performed by automatic high-pressure liquid chromatography with the same calibrator lots as used in the DCCT to facilitate comparisons with this study. Normal range for HbA_{1c} for the method at Steno Diabetes Center was 4.4 – 6.3 % (about 0.3 % higher than the DCCT method).

C-peptide **-** After 1, 6, and 12 month of diabetes, a standard liquid meal was utilized to stimulate endogenous C-peptide release (17). Serum samples were labelled and frozen at – 20 °C until shipment on dry ice to Steno Diabetes Centre for the determination of C-peptide within ½ year. Samples were thawed only once for RIA determination. Serum C-peptide was analyzed by a fluoroimmunometric assay (AutoDELFIA™ C-peptide, PerkinElmer Life and Analytical Sciences, Inc, Turku, Finland). The analytical sensitivity was better than 5 pmol/l, intra-assay coefficient of variation below 6 % at 20 pmol/l, and recovery of standard, added to plasma before extraction, about 100 % when corrected for losses inherent in the plasma extraction procedure.

Statistics: HbA_{1c} and insulin dose cannot be considered separately as the measured HbA_{1c} will be influenced by the insulin dose as well as by the residual beta-cell function. The idea was to combine the two in order to suggest a new measure of insulin-dose adjusted HbA_{1c} (IDAA1c) being relatively less influenced by treatment policy. A unified suggestion, in which both HbA1c and insulin dose were included, was investigated by multiple regression analysis with the logarithm of stimulated C-peptide as the dependent variable and gender, age, HbA_{1c} and daily insulin dose (U/kg bodyweight) as independent variables 6 and 12 months after diagnosis.

In the DCCT trial a limit of 300 pmol/l was defined as the level for "the C-peptide responders" (200-500 pmol/l). We aimed at defining PR in alignment with the DCCT (17) as an IDAA1c predicting a C-peptide response of >300 pmol/l.

To investigate the influence of age on the proportion in remission the insulin requirement and HbA_{1c} values during the follow-up were analysed with the patients divided into age groups (0-4.9, 5.0-9.9, 10.0-16yrs). Age group comparisons versus IDAA1c ≤ 9 was done by Chi-Square test for the count of patients.

To compare the various definitions the proportion of children in PR as defined by each definition was evaluated at 3, 6, 9 and 12

months. The insulin dose used to calculate the rate of PR was the value before the visit because HbA_{1c} reflects the blood glucose level over the previous 4 to 6 weeks period (8).

A statistical comparison was conducted to evaluate the concurrent agreement of HbA1c, IDAA1c, and stimulated C-peptide. Agreement between the definitions was examined by plotting twelve months values for stimulated C-peptide against both HbA1c and IDAA1c and with summary statistics for percentage agreement with stimulated C-peptide. This was supplemented with a formal Chi-Square test of which parameters HbA1c or IDAA1c that are most closely related to C-peptide, by constructing the 2 by 2 by 2 table of classifications based on HbA1c, IDAA1c and stimulated C-peptide. In this table, it was tested whether HbA1c ≤ 7.5 or >7.5 had an influence on stimulated C-peptide, when the IDAA1c classification was included. This consists for each IDAA1c group (≤ 9, respectively >9) a test of independence of HbA1c group and stimulated C-peptide group. A similar test was done with HbA1c and IDAA1c with reversed roles. The two test statistics were then added to obtain a joint conclusion which of the two measures gives the best agreement with the C-peptide definition.

To confirm the validity of IDAA1c at 12 months duration the relationship of stimulated C-peptide and IDAA1c at 6 and 12 months was investigated by linear regression according to duration and IDAA1c but not gender and age.

To examine the predictive validity of IDAA1c, HbA1c and insulin dose data from 1 and 6 months were used in a multiple regression model (including covariates age and gender) to predict C-peptide responses (logarithmic scale) at 6 and 12 months, respectively.

To examine the agreement between the two definitions (IDAA1c ≤ 9% and stimulated C-peptide > 300 pmol/l) a Chi-Square test was performed in the 2 by 2 table of classifications based on IDAA1c and stimulated C-peptide.

The stability of the IDAA1c defined PR was investigated by comparing the number of subjects transiting into and out of PR defined by IDAA1c and by other definitions of PR over the period 6 to 12 months.

Statistical analyses were performed using SAS version 9.1 (SAS Institute, USA, Inc, Cary, NC, USA). A p-value of 0.05 or less was considered significant.

RESULTS

Partial remission defined by IDAA1c: The multivariate analysis showed a negative correlation between stimulated C-peptide, HbA_{1c} and insulin dose, with a significant effect of age (estimate 0.09/year, $p<0001$) but not gender (estimate comparing females to males -0.01, $p=0.91$) at 6 months after diagnosis. It would be natural to include an age effect in the formula, if the aim of the study had purely been to predict the stimulated C-peptide level. However, as the purpose was to suggest a new measure for remission it was anticipated that the suggested formula for IDAA1c could be useful on its own and therefore age was not included. From the regression coefficients at six months: HbA_{1c} –0.21 and insulin dosage –0.94 it was seen that there was a factor of about 4.4 between the coefficients for these parameters. The R^2 value was found to be 0.30. Results at six and 12 months were similar. This inspired the suggestion of a combined expression of insulin dose and HbA_{1c}, formulated as a specific definition of the insulin dose-adjusted HbA1c (IDAA1c) = HbA_{1c} (%) + 4 x [insulin dose (U/kg/24h)]. The factor of 4.4 was substituted by 4 to obtain simple numbers. Based on the slope of

the regression line between stimulated C-peptide, HbA1c and insulin dose a predicted C-peptide can be calculated from any given set of corresponding HbA1c and insulin dose. The distribution of patients according to individual HbA_{1c} and insulin dosages at 6 months duration are shown in Figure 1A, in which each diagonal red line correspond to one IDDA1c value. According to this model an IDAA1c threshold ≤ 9 correspond to a predicted level of >300 pmol/l for the corresponding stimulated C-peptide. This expression can be used as a qualitative measure of PR and in alignment with the DCCT "C-peptide responders" (200-500 pmol/l) we have chosen IDAA1c ≤ 9 to define PR. Other threshold values for IDAA1c could have been chosen corresponding to different predicted C-peptide values. Compared to the PR definition: insulin dose ≤ 0.5 U/kg/24 and HbA_{1c} ≤ 7.5% (rectangular dashed box), our definition has been extended with the triangular area above and to the right side of the dashed rectangle (Figure 1A). As an indicator of more aggressive insulin therapy at some of the centres, there are more cases placed in the triangle to the right of the dashed line that marks an insulin dose ≤ 0.5 U/kg/24h than in the upper triangle above the dashed line marking an HbA_{1c} ≤ 7.5%.

Partial remission by IDAA1c and influence of age: Figure 1B shows that age at onset influences the rate of PR in children with type 1 diabetes. Significantly ($p< 0.05$) fewer patients in the young age group (0-5 yrs) were in PR (3-9 months, $p<0.01$) compared to the older age groups. After 12 months only 5% of the very young children are in PR compared to 20% of the older age groups.

Comparison of partial remission by IDAA1c with existing definitions: The proportion of children in PR according to various definitions is shown in Figure 1C as a function of diabetes duration. As the HbA1c level at one month still reflects glycemia before diagnosis the comparison between the different definitions of PR was performed at 3 months. From 3 to 12 months the curves for IDAA1c (Curve 1), C-peptide (Curve 2) and insulin dose (Curve 4) show close agreement. The definition of PR including insulin dose ≤ 0.5 U/kg/24h and HbA_{1c} ≤ 7.5% (Curve 5) suggests that fewer are in PR and HbA_{1c} ≤ 7.5% without insulin dose adjustment (Curve 3) suggests that more patients are in PR after 3 months. Using the new definition, PR occurred in 61% at 3 months, in 44 % at 6 months and 18% after 12 months.

Agreements between HbA1c, IDAA1c, and stimulated C-peptide: The agreement between definitions of those in PR by HbA1c ≤ 7.5% and by IDAA1c ≤ 9 compared to residual beta-cell function with C-peptide >300 pmol/l, are shown in figure 1D. The definitions agree in the upper left quadrant and the lower right quadrant of the diagrams. However, for HbA1c (left panel) there are significantly more patients in the lower left quadrant of the diagram with an HbA1c ≤ 7.5% but with a residual beta-cell function ≤ 300 pmol/l than for IDAA1c (right panel), probably because the aggressively insulin treated children with low residual beta-cell function are more accurately accounted for in the dose adjusted model (see formal Chi-Square test below). A formal test of the strength of the relationship between each definition and stimulated C-peptide at 6 months, was performed in a model, where the classifications of PR according to both HbA1c and IDAA1c were allowed an effect on the C-peptide definition of PR (>300 pmol/l).

In the joint test, HbA1c was not significant (chi-square=2.40, 2 degrees of freedom, p=0.30), whereas IDAA1c was clearly significant (chi-square=11.07, 2 degrees of freedom, p=0.004).Thus IDAA1c gives the best agreement with the C-peptide definition. The same conclusion was reached after 12 months.

Correlation between IDAA1c and actual C-peptide response at 6 and 12 months: The relationship of IDAA1c and stimulated C-peptide at 6 and 12 months is shown in Figure 1 E. The regression curves suggest a tendency towards higher stimulated C-peptide values at 6 months compared to 12 months, also when related to IDAA1c. Overall, the predictive value of IDAA1c in combination with gender and age was good (R^2 0.30 at 6 months, and 0.31 at 12 months)

IDAA1c at 1 and 6 months as predictor of future values of C-peptide response: Predicting C-peptide after 6 months based on one month data, as well as after 12 months based on 6 month data, using gender, age, HbA1c and insulin dose, it was found that there was a significant dependence on both HbA1c and insulin dose, but the effect of these could be adequately summarized by the IDAA1c. The coefficients in the final model for predicting (log) C-peptide after 12 months was gender (estimate for females -0.11, p=0.40), age (estimate 0.13, p<0.001) and IDAA1c after 6 months (estimate -0.32, p<0.001).

Stability of IDAA1c defined PR in the prepubertal compared to older age groups: Only a few of the very young children (0-4 years) are in PR using any of the two definitions (stimulated C-peptide >300 pmol/l or IDAA1c ≤ 9). The older children (10-16 years) have relatively higher C-peptide values, thus the patients, who are in PR according to C-peptide, but not IDAA1c are mostly older presumably with more insulin resistance due to puberty, whereas those that are not in PR according to C-peptide, but in PR according to IDAA1c are in the prepubertal group (5-9 years) with better insulin sensitivity. The two definitions agree for 71.4 % of the prepubertal and the older group of patients (average for 6 and 12 months values)

Stability of the definitions: During the period 6 to 12 months after diagnosis, the change in frequency of PR as assessed by IDAA1c, HbA1c, insulin dose and stimulated C-peptide , is illustrated in Table 1. Using the IDAA1c ≤ 9 only 1 patient entered PR and 61 ended PR; using HbA1c ≤ 7.5 %, 15 entered PR and 53 ended; using insulin dose ≤ 0.5 U/kg/24h 5 entered and 66 ended and using stimulated C-peptide (>300 pmol/l) 9 entered PR and 49 ended.

CONCLUSIONS

We have suggested a novel definition: HbA_{1c} (%) + [4 x insulin dose (U/Kg/24h)] ≤ 9 for the PR period in children and adolescents with type 1 diabetes (Figure 1 A). This practical and simply calculated definition is useful as it relates insulin dose and measured HbA1c to the preservation of beta-cell function (C-peptide levels). This measure, adjusting for the exogenous insulin, can be used as a quantitative measure of the underlying and theoretically untreated disease and it is in this setting superior to a definition using HbA_{1c} alone.

This definition also avoids the necessity of measuring C-peptide levels, which is laborious, expensive and often unavailable. Generally, there is good agreement between these two measures IDAA1c and C-peptide (Figure 1 C), although we see a different pattern over age (Figure 1B,E), as discussed below. Using either HbA1c ≤ 7.5% or IDAA1c ≤ 9 the maximum PR in all age groups is reached at around 3 months after diagnosis (Figure 1B), which is in accordance with other studies (11,18). In addition, the IDAA1c correctly identifies those in PR from the very start whereas a PR definition by insulin dosage ≤ 0.5U/kg/24h misclassifies a proportion early in the disease due to lack of or delay in insulin treatment around the time of diagnosis (Figure 1C). This may be of importance for selection of patients into intervention studies aimed at protecting islet cell function.

Because IDAA1c is based on a joint evaluation of C-peptide, HbA1c and insulin dose, the agreement of those in PR by the C-peptide definition is better for IDAA1c than for HbA1c alone (Figure 1D) which was also shown in the chi-square test of the relationship between the two measures and stimulated C-peptide.

Interestingly, the residual beta cell function was highest in the age group 10-15 yrs during the whole study period and this is comparable with the observations of the US multicenter national study group Type 1 diabetes Trial Net (13). Despite this, the new definition indicates that the frequency of PR was not higher in this group of patients compared to the school age children 5-10 yrs old. Likewise the mean daily insulin dose was higher in the older age group (10-15 yrs) than in the younger (5-10 yrs) perhaps indicating higher insulin resistance during puberty (19). Thus the degree of hyperglycemia is not determined only by the beta-cell function or insulin resistance but results from a combination of these two factors which is reflected in the new definition. Therefore IDAA1c was in agreement with stimulated C-peptide in 71.4 % of those in PR of the prepubertal and older patients (1E)

It is important to know the relationship of IDAA1c and stimulated C-peptide during the first year in new onset type 1 diabetes. Overall IDAA1c showed a good correlation with the residual beta cell function as assessed by stimulated C-peptide (R^2 31%). This agreement level compares well with the homeostasis model assessment (HOMA) (14) where estimates of beta-cell function correlated with hyperglycaemic clamp (37%) and to the intravenous glucose tolerance test (41%) . In addition IDAA1c at 6 months was the best predictor of stimulated C-peptide concentrations at 6 and 12 months compared to HbA1c and insulin dose. This shows that IDAA1c overall is a good estimate of stimulated C-peptide in type 1 diabetes.

In terms of stability over time, only one patient was found to enter PR between 6 and 12 month duration. When spontaneous PR occurs in pre-pubertal or pubertal patients, it occurs most often within the first 4 months, and infrequently after 6 months (20,21). This is a strong endorsement of the new IDAA1c definition as all other definitions discussed have higher number of patients that appear to enter PR in the period 6 to 12 months (Table 1).

The new formula is very easy and practical to use in the daily clinic where a diabetes nurse specialist takes care of many aspects of daily management, during the first months after diagnosis. At each visit in the outpatient clinic the IDAA1c can be calculated by the nurse to check that the patient is still in remission particularly if they do not frequently measure blood glucose or record data. If this is not the case the patient may need to be referred to a pediatric diabetologist for changes in insulin management. Already this has improved the delivery of diabetes care in some of our clinics and leads to a smooth transition to more individual treatment regimens.

Direct measurement of C-peptide has been recommended to provide the most appropriate primary outcome in trials evaluating the efficacy of therapies to preserve beta-cell function (13). The new IDAA1c should be beneficial for research in this area as it might remove the need for intrusive investigations. It takes into account the glycemic consequences of a change in residual beta cell function. C-peptide measurements alone do not provide this information. In addition the model should make it easier to select children and adolescents with a significant endogenous insulin production and evaluate clinically meaningful changes in intervention therapies (22) that are aimed at preserving/regenerating beta cell function in new onset type 1 diabetes.

In conclusion, the new insulin dose adjusted definition of the partial remission period gives the best agreement with the stimulated C-peptide definition, is convenient and easy to use and is associated with a stimulated C-peptide response of >300 pmol/l.

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Table 1: PR transitions from 6 to 12 months
Number of patients according to PR status at 6 and 12 months (per cent among patients according to state at 6 months).

	In PR at 6 months	Not in PR at 6 months
PR definition	Proportion in PR at 12 months	Proportion in PR at 12 months
IDAA1c ≤ 9 %	37/98 (38%)	1/122 (1%)
HbA1c ≤ 7.5 %	87/140 (62%)	15/85 (18%)
Insulin dose ≤ 0.5 U/kg/24h	46/112 (41%)	5/123 (4%)
C-peptide > 300 pmol/l	58/107 (54%)	9/119 (8%)

Figure 1A
The thresholds for PR remission based on IDAA1c ≤ 9 (solid green line) and HbA1c ≤ 7.5 % and insulin dosages ≤ 0.5 U/kg/24h (rectangular dashed box). Each diagonal red line correspond to one IDAA1c value. The numbers in boxes are the predicted values for stimulated C-peptide concentrations for a ten-year old boy at the relevant IDAA1c value and as illustrated other thresholds values for IDAA1c correspond to different predicted C-peptide values. The + signs give the distribution of 257 cases of type 1 diabetes after 6 months duration.

Figure 1B.
Age at onset influences the rate of PR as assessed by IDAA1c in children with type 1 diabetes. The proportion of PR is lowest in the youngest age group (0-4.9 years). Due to lower insulin sensitivity the proportion of PR in the old age group (≥10 years) and the school age children (5-9.9 years) appears similar despite higher residual beta cell function.

Figure 1C
The proportion of children in PR according to the different definitions. From 3 to 12 months the curves for IDAA1c (Curve 1), C-peptide (Curve 2) and insulin dose (Curve 4) show close agreement.Using the new definition, PR occurred in 61% at 3 months, in 44 % at 6 months and 18% after 12 months.

Figure 1D
The agreement between definitions of those in PR, HbA1c ≤ 7.5% (left panel, dashed vertical line), IDAA1c ≤ 9 (right panel, dashed vertical line) and stimulated C-peptide >300 pmol/l (dashed horizontal line) at 12 months. The arrows point to the areas showing that HbA1c ≤ 7.5 disagree significantly more than IDAA1c ≤ 9 with the C-peptide >300 pmol/l probably because the children receive more exogenous insulin which is accounted for in the insulin dose adjusted model.

Figure 1E
The relationship of IDAA1c ≤ 9 (dashed vertical line) and stimulated C-peptide >300 pmol/l (dashed horizontal line) at 6 and 12 months. Individual observations are shown by age groups. The regression lines 6 (solid) and 12 (dashed) months show the linear correlation of IDAA1c and C-peptide over a continuum of stimulated C-peptide values.

Fig. 1A

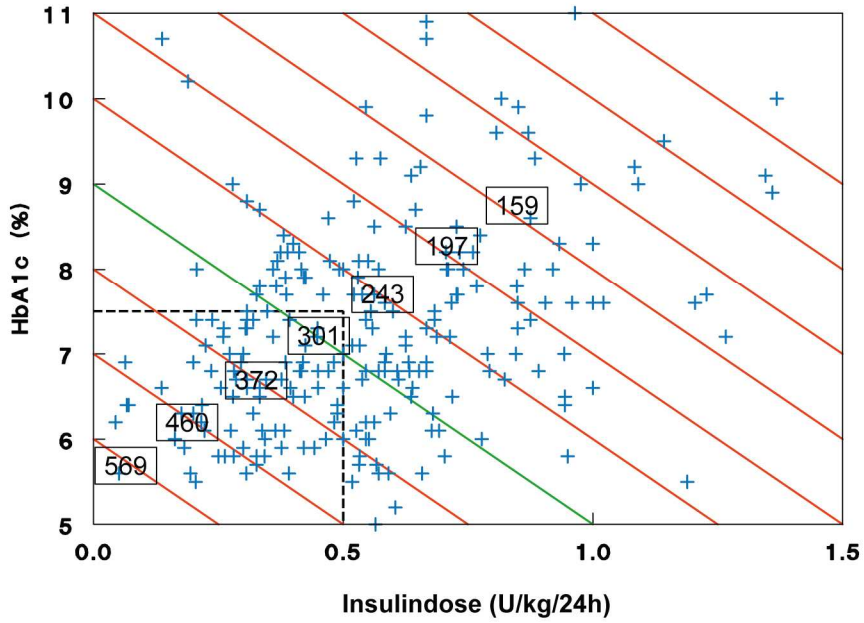

HbA1c (%)
11
10
9
8
7
6
5
0.0
0.5
1.0
1.5
Insulindose (U/kg/24h)
159
197
243
301
372
460
569

Fig. 1B

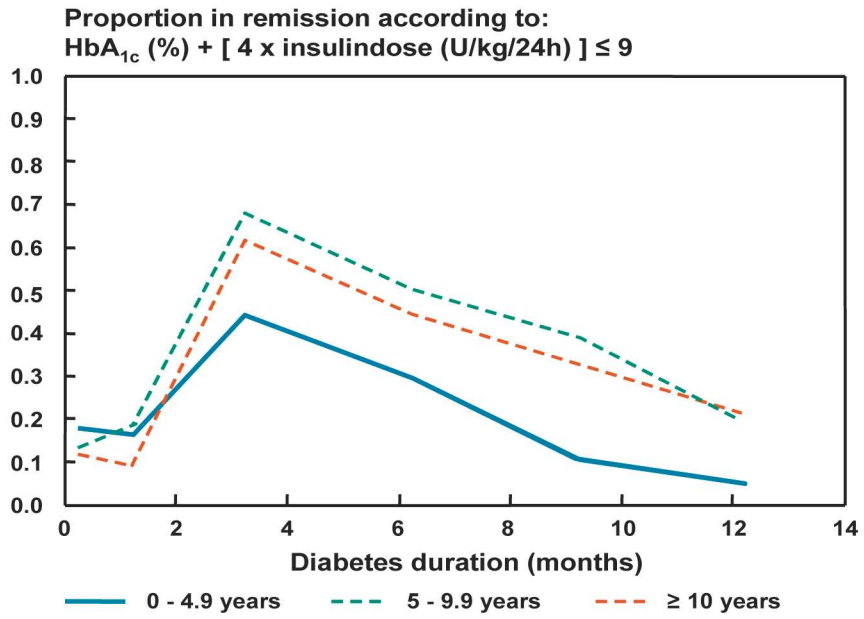

Proportion in remission according to:
HbA1c (%) + [4 x insulindose (U/kg/24h)] ≤ 9
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0
2
4
6
8
10
12
14
Diabetes duration (months)
0 - 4.9 years
5 - 9.9 years
≥ 10 years

Fig. 1C

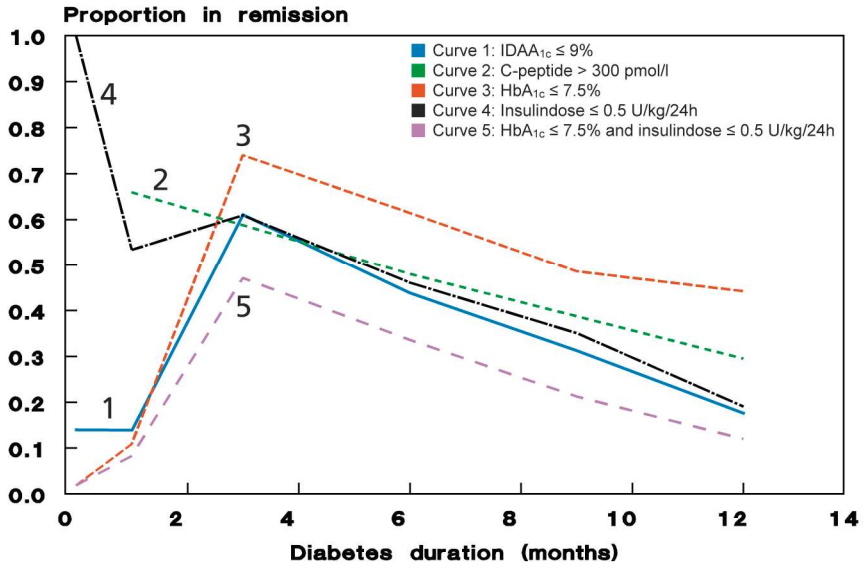
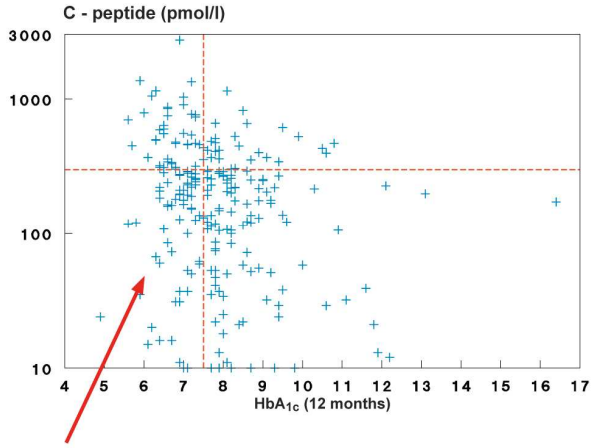
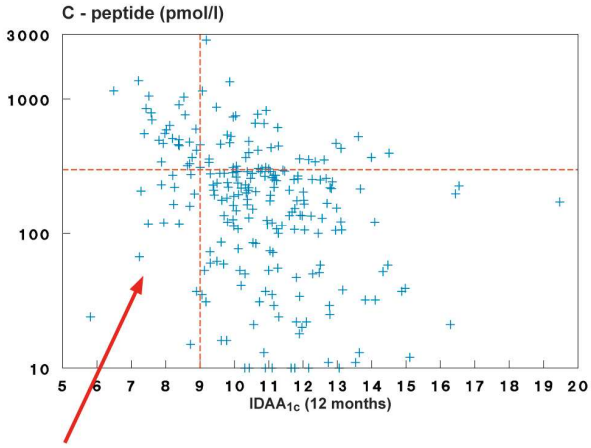


Fig. 1D

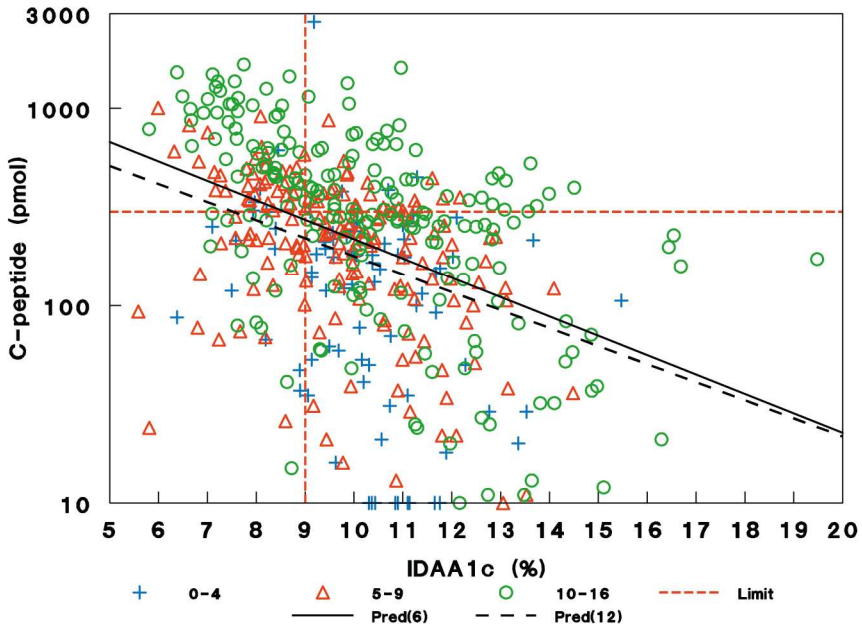


Remission according to HbA_{1c}, but not C-peptide



Remission according to $IDAA_{1c}$, but not C-peptide

Fig. 1E


3000
1000
100
10
C-peptide (pmol)
5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20
IDAA1c (%)
0-4
5-9
10-16
Limit
Pred(6)
Pred(12)